

EUS-FNA and EBUS-TBNA in pulmonary medicine: consensus report of the Belgian Working Party for thoracic endoscopy

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Summary

Obtaining a pathological diagnosis of intrathoracic lesions and obtaining accurate mediastinal staging information from patients with non-small cell lung cancer (NSCLC) remain true challenges in pulmonary medicine. Recently, two new techniques have been introduced that challenge current practice, namely the curved-linear transoesophageal endoscopic ultrasound with real time guided fine-needle aspirations (EUS-FNA) and curved-linear endobronchial

ultrasound with real time guided transbronchial needle aspirations (EBUS-TBNA). These techniques are designed to be performed without general anaesthesia and thus as out-patient procedures. Taking into account the available evidence, the consensus report of the Working Party for Thoracic Endoscopy of the Belgian Thoracic Society on the role of EUS-FNA and EBUS-TBNA in pulmonary medicine anno 2009 is reported.

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Introduction

Pathological examination of pulmonary tissue is important for a plethora of lung diseases. Tissue is necessary to obtain a pathological diagnosis, or in case of lung cancer, to obtain clinical staging information (lymph node invasion and metastasis). Sputum examination, bronchoscopy with tissue sampling, ultrasound or CT-guided trans-thoracic needle aspirations (TTNA) and surgical biopsies represent the classical armamentarium for the chest physician. New technical developments in echo-endoscopy have become available that improve the possibilities to obtain pulmonary and mediastinal tissue in a non-surgical way. Firstly, radial ultrasound miniprbes can be introduced through the biopsy channel of a bronchoscope to perform endobronchial ultrasonography. These miniprbes are available in some

expert centers for several years and can guide the sampling of more peripheral pulmonary lesions and help for the evaluation of invasiveness of radio-ocult central lesions. Secondly, and more recently the curved-linear transoesophageal endoscopic ultrasound with real time controlled fine-needle aspirations (EUS-FNA) and curved-linear endobronchial ultrasound with real time controlled transbronchial needle aspirations (EBUS-TBNA) have been introduced (*Figure 1* on page 317).

According to the need for anaesthesia and the interventional risk, the available methods can be classified as non-invasive, minimally invasive or invasive (*Table 1* on page 317). Minimally invasive techniques such as EUS-FNA and EBUS-TBNA are developed to be performed without general anaesthesia, but require local (throat) anaesthesia with or without mild sedation.

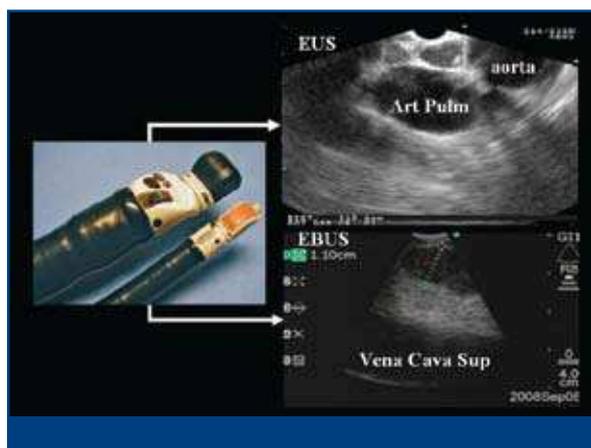


Figure 1. Curved linear EUS and EBUS endoscopes (left panel) and a respective image obtained during endoscopy. These endoscopes enable the real-time guided puncture of mediastinal and pulmonary structures. The EUS endoscope is larger as compared to the EBUS endoscope. The image obtained with EUS covers a larger area and is of better quality than that obtained with EBUS.

A substantial body of clinical evidence now supports the implementation of EUS-FNA and EBUS-TBNA in pulmonary medicine. The main reason is that these techniques have a measurable impact on clinical practice in terms of avoided surgical (e.g. mediastinoscopy, video-assisted thoracoscopic surgery, thoracotomy) and non-surgical (e.g. CT-guided transthoracic punctures) interventions. This document focuses on the current role of the endoscopic ultrasound techniques that enable real time controlled needle aspirations (EUS-FNA and EBUS-TBNA) in pulmonary medicine.

Methodology

Because EUS-FNA and EBUS-TBNA are two techniques that are expected to be more widely implemented by chest physicians in the coming years, the Working Party for Thoracic Endoscopy of the Belgian Thoracic Society decided to provide a consensus document based on a literature study and adapted for the Belgian situation. Because of space limits, only those papers most relevant for the Belgian situation have been included in the reference list. A level of recommendation is proposed for each indication (*Table 2*). This level is adapted from the report of the American College of Chest Physicians (ACCP) task force.¹ The grading system is composed of only two types of recommendation (1= strong and 2= weak) and takes into account

Table 1. Available diagnostic procedures.

Non-invasive	Minimally invasive	Invasive
Sputum analysis	Bronchoscopy*	Open lung biopsy
	TTNA	Mediastinoscopy
	EBUS-TBNA	VATS
	EUS-FNA	

*TTNA: transthoracic needle aspiration; EBUS-TBNA: endobronchial ultrasound with transbronchial needle aspiration; EUS-FNA: transoesophageal endoscopic ultrasound with fine needle aspiration; VATS: video-assisted thoracoscopic surgery. *Bronchoscopy with either (a combination of) central/peripheral biopsies (guided or not by fluoroscopy, radial ultrasound miniprobes or electromagnetic navigation), 'blind' TBNA, brushing, washing.*

two dimensions: the strength of evidence and the balance between benefit vs risk/burden of the intervention (*Table 2*). The benefit-to-harm ratio includes consideration of the clinical advantage, quality of life, burden, risk and cost whenever applicable, identifiable and determinable. This document is the result of a joint effort of the members of the working party. The Belgian Thoracic Society only provided logistic support, there was no commercial involvement.

Technique and organisation for EUS-FNA and EBUS-TBNA

Both EUS-FNA and EBUS-TBNA should be performed as outpatient procedures in the bronchoscopy suite, equipped at least with an automatic monitoring unit for peripheral saturation and pulse.^{2,3} Both procedures require the presence of one dedicated and well trained physician and a nurse.

Before starting the procedure, the patient should be well informed by the endoscopist. Global safety guidelines for endoscopic ultrasound follow those for a regular endoscopic procedure. In general, patients without a history of a coagulopathy do not require coagulation tests, but cautiousness is warranted. Whereas low dose aspirin is not a problem for either EUS-FNA or EBUS-TBNA, other anticoagulants such as clopidogrel and warfarin must be withdrawn at least one week before the procedure and adequate coagulation tests should be within normal ranges when considering these procedures. For EUS-FNA, it is important to ascertain that the patient can be placed comfortably on the left side (attention for shoulder or hip problems) and that

Table 2. Evidence levels: 'Good' is based on randomized controlled trials (RCT) without important limitations or based on overwhelming evidence from observational studies; 'Moderate' is based on RCT with limitations or strong evidence from observational studies; 'Poor' is based on observational studies and case series. Benefit versus risk and burden: 'Benefit-to-harm ratio imbalanced' if the advantages of a procedure are greater than the disadvantages or if the disadvantages of a procedure are greater than the advantages; 'Benefit-to-harm ratio balanced' if the benefits and harms are more evenly balanced, and thus recommendations cannot be as strong and patient preference plays a larger role; 'Uncertain' if the balance of benefits and burden is unclear.

	Good evidence	Moderate Evidence	Poor Evidence
Benefit-to-harm ratio imbalanced	1A	1B	1C
Benefit-to-harm ratio balanced	2A	2B	2C
Uncertain	-	-	2C

swallowing represents no problem so introduction of the endoscope will be possible and well tolerated. For EBUS-TBNA, it is important to ascertain that the patient can lay on his back comfortably. We recommend for both procedures to administer 1-2 litre supplemental oxygen per minute via a nasal canula in order to have a peripheral oxygen saturation before and during the procedure above 90%. If the patient has bronchial asthma, it is recommended to administer 100-400 µg salbutamol 10 minutes before the EBUS-TBNA procedure. In case sedation is necessary, an intravenous line is required in advance. Anaesthesia differs for EUS-FNA versus EBUS-TBNA. Local throat anaesthesia is needed (e.g. xylocaine spray) for both. In case of EUS-FNA, the oesophagus needs additional treatment with lidocaine gel (administered orally). For EBUS-TBNA the large airways are further anaesthetized with xylocaine administered through the bronchoscope in small aliquots. In over half of the patients, EUS-FNA, but not EBUS-TBNA, can be performed without sedative medication. If sedation is used, we recommend the use of midazolam for both EUS-FNA and EBUS-TBNA. Fentanyl can be used as an adjunct to midazolam. When using sedative medication, the antidotes must be present in the bronchoscopy suite. We do not recommend the routine use of prophylactic antibiotics to prevent endocarditis although under certain circumstances (e.g. prosthetic heart valves, history of endocarditis) this can be considered (evidence poor, benefit or risk and harm ratio is uncertain, recommendation level 2C).

Endothoracic lesions (primary lung tumours, metastatic lesions from extrathoracic malignancies) and/or mediastinal and hilar lymph nodes can be visualized with either EUS-FNA and/or EBUS-

TBNA. The indication (diagnosis versus staging; see below), the localisation of the lesion, the test characteristics, the availability and expertise, and patient preference can all codetermine which procedure is performed and whether only one target lesion has to be sampled rather than a systematic scanning and sampling. The ultrasound imaging frequency (adjustable between 5-10 Mhz) and depth of ultrasonographic view (adjustable between 2-8cm) allow the optimization of the image. Specific ultrasonographic features associated with malignancy of lymph nodes (such as the round shape, the homogenous hypoechogenic ultrasound pattern and the sharp edges) have been described, but a needle aspiration of the lesion is always required as tissue diagnosis is more accurate than imaging alone.⁴ For EUS-FNA, a 21-G needle is used while for EBUS-TBNA a 22-G needle is currently available. Suction can be applied by means of a 5-10 cc vacuum syringe once the needle is into the target lesion, but it is unclear if this really improves the quality of the fine needle aspirates. A 19-G histology trucut needle exists for EUS-FNA, however, there is no clear advantage and probably a higher risk of bleeding for the latter. In case rapid on site evaluation (ROSE) by a cytotechnician or pathologist is available, the endoscopist can proceed until representative samples are obtained.^{4,5} When this is not the case, it has been shown that 3 punctures per lymph node station is sufficient.⁶ Although formal data are lacking, a number of 3 punctures for targets other than lymph nodes is proposed in case ROSE is not available. Once the procedure has terminated, the patient is observed for at least one hour. In case sedation was given, we advise not to drive a car or to handle technical equipment that same day.

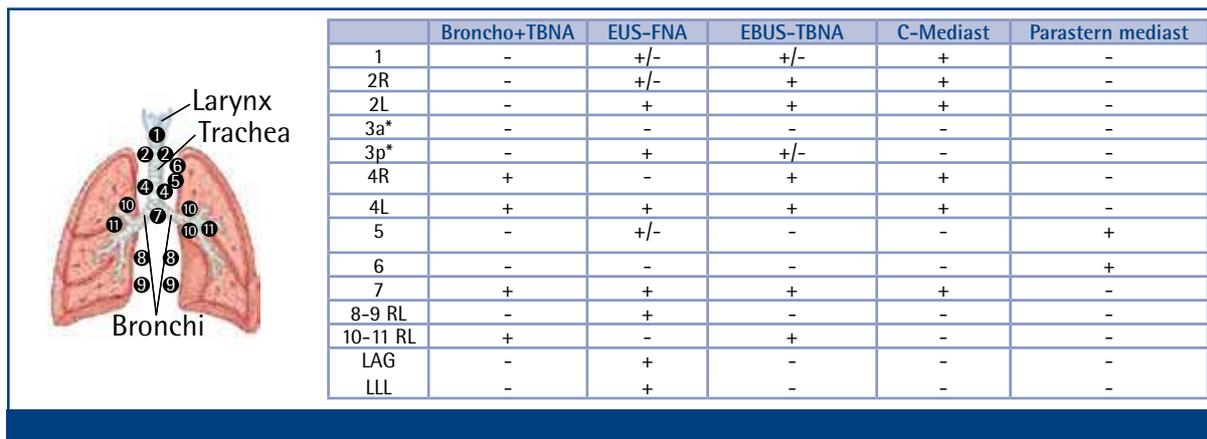


Figure 2. Diagnostic performance is mainly determined by the localisation of the target lesion (Mountain Dressler lymph node map). *Broncho*: bronchoscopy; *TBNA*: transbronchial needle aspiration; *EUS-FNA*: transoesophageal endoscopic ultrasound with real time guided fine needle aspiration; *EBUS-TBNA*: endobronchial ultrasound with real time guided transbronchial needle aspiration; *C-mediast*: cervical mediastinoscopy; *Parastern mediast*: parasternal mediastinoscopy; *R*: right; *L*: Left; *LAG*: left adrenal gland; *LLL*: left liver lobe; *+*: easily reachable; *+/-*: exceptionally reachable; *-*: not reachable; **3a/3p*: prevascular and retrotracheal respectively.

Indications for EUS-FNA and EBUS-TBNA in pulmonary medicine

Both EUS-FNA and EBUS-TBNA are endoscopic ultrasound techniques that allow the real time guided needle sampling of lesions located outside but adjacent to the organ the scope is placed in. As a consequence, EUS-FNA and EBUS-TBNA are complementary techniques with a reach that is only partially overlapping (Figure 2).

EUS-FNA and EBUS-TBNA can be performed for two main reasons. The first is to obtain a (histo- or cytopathology) *diagnosis* of an intrathoracic lesion. The second reason is to obtain *clinical staging* information in case of a known intra- or extrathoracic malignancy.

Obtaining a diagnosis with EUS-FNA or EBUS-TBNA

The clinician can consider EUS-FNA or EBUS-TBNA as minimally invasive extensions of the available armamentarium (Table 1 on page 318) to obtain a diagnosis of an intrathoracic lesion after a negative standard bronchoscopy (with or without biopsy and “blind” TBNA). The choice to perform EUS-FNA or EBUS-TBNA is determined by a range of factors discussed above. FNA and TBNA samples are cell-suspensions and/or smears. Immunohistochemistry and microbiology can be performed as adjunct in the diagnostic course.

- EUS-FNA or EBUS-TBNA can be considered for a *centrally located parenchymal lung lesion* that

needs tissue verification after a standard fiber- or videobronchoscopy that did not yield a diagnosis because of the localisation “outside” of the central airways (evidence poor, benefit outweighs risk and burden, recommendation level 1C). These lesions are hardly amenable for (CT-guided) transthoracic needle aspirations because these centrally located lesions confer a high risk for pneumothorax. As such, EUS-FNA or EBUS-TBNA can be indicated to diagnose primary (non-small cell and small cell) lung cancer but also to obtain a diagnosis in patients with extra-thoracic malignancies by puncture of a presumed intrathoracic metastatic lesion.^{7,8} Immunohistochemistry can be helpful in the differential diagnosis of many cancers.

- EUS-FNA or EBUS-TBNA can be considered in patients with a *suspicion for intra- or extrathoracic malignancy with enlarged or FDG-positive hilar or mediastinal lymph node(s)* (evidence moderate, benefit outweighs risk and burden, recommendation level 1B). Literature supports that EUS-FNA or EBUS-TBNA can be used to diagnose lung cancer by puncture of the suspect metastatic lymph node.^{4,9,10} Immunohistochemistry on the samples obtained from the presumed intrathoracic metastatic lesion can be helpful to obtain a diagnosis and to document on the origin of the primary lesion.
- EUS-FNA or EBUS-TBNA can be considered in patients with a *suspicion for granulomatous diseases and enlarged hilar or mediastinal lymph node(s)*

(evidence moderate, benefit outweighs risk and burden, recommendation level 1B). Literature supports that EUS-FNA or EBUS-TBNA can be used to diagnose sarcoidosis and tuberculosis. The sensitivity to demonstrate sarcoidosis has been suggested in prospective series to be 80-90%.¹¹⁻¹³

- EUS-FNA or EBUS-TBNA can be considered in case of a *mediastinal lesion or mass* that needs tissue verification, such as suspected small cell and non-small cell lung carcinoma. The evidence for other epithelial tumors (such as thymic carcinoma, teratocarcinoma, germ cell tumour), sarcomas (e.g. chondrosarcoma, teratosarcoma) and even for mediastinal goiters is however faint because this evidence is mainly based on case reports (evidence poor, benefit outweighs risk and burden, recommendation level 1C). We recommend against the routine use of EUS-FNA or EBUS-TBNA in case there is a high clinical suspicion for lymphoma or a primary mediastinal tumor (evidence in favour of EUS-FNA or EBUS-TBNA is poor, benefit uncertain, recommendation level 2C). Although a fine needle cytology can yield a definite diagnosis of lymphoma, cytology doesn't give information about tumour architecture and specific typing can be difficult for the majority of lymphomas because of lack of material.¹³ EUS or EBUS can be very helpful in imaging and identifying cystic mediastinal lesions; however, puncture in these is not advocated because of the risk for mediastinitis (evidence poor, risk outweighs benefit, recommendation level 1C).
- EUS-FNA can be used in patients with a clinical suspicion of thoracic malignancy in whom imaging (CT or FDG-PET/CT) suggests *left adrenal gland (LAG) or left liver lobe (LLL)* metastasis (evidence poor, benefit outweighs risk and burden, recommendation level 1C). By approaching the LAG/LLL by EUS-FNA, one can obtain a diagnosis and a clinical staging with a single procedure.¹⁴

Obtaining cancer staging with EUS-FNA or EBUS-TBNA

To obtain clinical staging information of either intra- or extrathoracic malignancies, EUS-FNA or EBUS-TBNA can be considered. The routine use of the curved linear EUS-FNA or EBUS-TBNA endoscopes for assumptions regarding direct mediastinal invasion by the primary tumour is not recommended. The curved linear probes have an operating frequency which is too low (5-10 MHz) resulting in

ultrasound images that do not allow a confident discrimination of different tissue layers.

EUS-FNA or EBUS-TBNA for staging extrathoracic malignancy

- EUS-FNA or EBUS-TBNA can be considered in patients with a known extrathoracic malignancy presenting with a *centrally located parenchymal lung lesion* suspicious for metastasis that requires tissue verification (evidence poor, benefit outweighs risk and burden, recommendation level 1C). These are the patients who are hardly amenable for transthoracic needle aspirations. The evidence for proposing EUS-FNA or EBUS-TBNA is however indirect and relies on that published for diagnosing lung cancer.^{7,8}
- EUS-FNA or EBUS-TBNA can be considered in a patient with known extrathoracic malignancy presenting with *mediastinal and/or hilar lymph nodes* suspicious by size or FDG-uptake for lymphogenic metastasis and requiring tissue verification (evidence moderate, benefit outweighs risk and burden, recommendation level 1B).¹⁵ The evidence for proposing EUS-FNA or EBUS-TBNA is indirect and relies on the evidence published for the diagnosis and staging of lung cancer.^{4,9,10}

EUS-FNA or EBUS-TBNA for staging NSCLC

The accurate mediastinal staging is of utmost importance in patients with NSCLC who had a negative evaluation for distant metastases. The reason is that the mediastinal tumour stage guides optimal treatment strategy. A large number of studies have been published on mediastinal staging, however, differences in hypotheses, design, inclusion criteria and gold standards often make it difficult to compare the different invasive and minimally invasive tests.

The ACCP has translated the available evidence on invasive mediastinal staging into a practice guideline.¹⁶ It is to note that minimally invasive techniques such as EUS-FNA and EBUS-TBNA are firmly incorporated in the 2nd edition of this guideline. Four patient groups were defined with respect to intrathoracic CT-characteristics of the primary tumour and the mediastinum. Based on this categorization, the need for an invasive test and selection of the best test was proposed. This ACCP guideline was considered a basis to guide and discuss individual patient assessment.

- Group A: For patients with unmistakable extensive mediastinal infiltration of the tumour, CT

assessment of the mediastinal stage is usually sufficient and no invasive confirmation of the mediastinal stage is warranted (evidence poor, benefit outweighs risk or harm, recommendation level 1C). The only issue in these patients is to obtain a diagnosis. Although sputum cytology and bronchoscopy with or without TBNA are valuable, EUS-FNA or EBUS-TBNA are possible alternatives (see above, 'obtaining a diagnosis with EUS-FNA or EBUS-TBNA').

- Group B: For patients with discrete mediastinal lymph node enlargement (short-axis diameter \geq 10 mm on a transverse CT scan image), invasive confirmation of the CT graphic stage is recommended (regardless of whether a PET is positive or negative in the mediastinal nodes). Both endoscopic ultrasound techniques can be recommended to approach these enlarged mediastinal lymph nodes (evidence moderate, benefit outweighs risk or harm, recommendation level 1B).^{7;10;17;18} Unfortunately, the ACCP guideline does not take into account the minimal criteria for a complete mediastinal evaluation. In the ESTS guidelines, it is proposed that a minimum of 3 mediastinal lymph node stations - or lymph node mapping - should be evaluated (left and right paratracheal and subcarinal).¹⁹ In fact, the ACCP guideline incorporates EUS-FNA and EBUS-TBNA based on evidence where the median number of investigated lymph nodes was one rather than three. Although it is recommended to start sampling with the contralateral (N3) nodes after which one can proceed to the N2 nodes, one could argue that with EUS-FNA or EBUS-TBNA, the mediastinal staging is often incomplete. Preliminary data suggest that a combination of EUS-FNA plus EBUS-TBNA might overcome this issue and ongoing trials will provide additional answers.²⁰ On the other hand, evidencing lymph node invasion in the pre-operative phase leads to the cancellation of (immediate) surgery and directs the treatment towards induction therapy.²¹
- Patients with a peripheral tumour and normal sized mediastinal lymph nodes (short-axis diameter < 10 mm) that show FDG uptake on PET are considered group C in the ACCP guideline (no enlarged lymph nodes). The ACCP guideline suggest a mediastinoscopy in these patients. The Belgian consensus text proposes to reclassify them in group B, recommending an endoscopic staging technique as a possible first choice (evidence moderate, benefit outweighs risk and harm, recom-

mendation level 1B). The reason is that the high prevalence of malignancy and technical feasibility in experienced hands to perform needle aspirations in normal sized lymph nodes have shown to result in high sensitivities (80-90%) for both EUS-FNA and EBUS-TBNA.²²⁻²⁴

- Group C: For patients with a central tumour or clinical N1 lymph node (enlarged or with FDG uptake) but a normal mediastinum, invasive mediastinal staging is recommended (regardless of FDG-PET findings). Although the ACCP guidelines state that endoscopic ultrasonography may be a reasonable strategy, the Belgian working party is more reluctant (evidence moderate, benefit versus burden is balanced, recommendation level 2B). Firstly, and as suggested above, both fine needle techniques are unsuited to perform systematic sampling as a single procedure. Secondly, the prevalence of malignancy in the mediastinal lymph nodes is low (10-20%) in these patients. Thirdly, the negative predictive value of the minimally invasive needle aspirations is suboptimal (around 80%). A low prevalence of malignancy combined with a suboptimal negative predictive value of needle aspirations by minimal invasive techniques translates into additional "confirmatory" surgical procedures in a large amount of the patients in this group C, which is cost-generating. Therefore, it seems more logic to propose a mediastinoscopy here (evidence moderate, benefit outweighs risk or harm, recommendation 1B). Again, whether the combination of EUS-FNA plus EBUS-TBNA is an alternative, is currently under investigation and is not recommended at this time for regular practice.²⁰
- Group D: For patients with a peripheral clinical stage I tumour, invasive confirmation of the mediastinal lymph nodes can be omitted only if a PET scan is negative in the mediastinum and hilum. The Belgian working party recommends against the use of EUS-FNA or EBUS-TBNA in these patients (evidence good, benefit large, recommendation level 1A).

EUS-FNA or EBUS-TBNA for restaging NSCLC

Although there are retrospective series available that show the feasibility and safety of EUS-FNA and EBUS-TBNA to perform clinical restaging after induction therapy was administered, there is insufficient evidence supporting firstly that invasive restaging is routinely indicated and secondly that EUS-FNA and/or EBUS-TBNA are the procedures of choice as

Table 3. contraindications for EUS-FNA and EBUS-TBNA

EUS-FNA	EBUS-TBNA
Patient cannot swallow	Respiratory Insufficiency
Oesophageal stenosis	Laryngeal or tracheal stenosis
Uncorrected coagulation disorder	Uncorrected coagulation disorder

the negative predictive value of these techniques is suboptimal.^{25,26} The Belgian working party therefore recommends against minimally invasive restaging in regular practice (evidence in favor of EUS-FNA or EBUS-TBNA is poor, benefit-to-harm and risk ratio uncertain, recommendation level 2C).

Contraindications for and risks/ complications associated with EUS-FNA and EBUS-TBNA

Although both EUS-FNA and EBUS-TBNA are considered safe procedures, knowledge of contraindications and potential complications contributes to the proper delineation of indications. Contraindications for EUS-FNA are essentially the same as those for a gastroscopy while contraindications for EBUS-TBNA are similar to those of a regular bronchoscopy (Table 3). If a patient cannot swallow or when an oesophageal stricture is present or when there is an uncorrected coagulation disorder, EUS-FNA is impossible. If a patient has respiratory insufficiency or a critical tracheal stenosis or an uncorrected coagulation, an EBUS-TBNA becomes impossible.

Complications have seldom been reported.²⁷ There is a minimal risk for *infection* (mediastinitis) with oral contaminants, both for EUS-FNA and EBUS-TBNA. The reason can be perforation of the sinus piriformis during introduction. Another reason for infection is that needles are passed through a biopsy channel that is not sterile due to the transpassing of the oral cavity. It seems that puncturing a mediastinal cyst is especially risky resulting in a formal advice not to puncture mediastinal structures that by ultrasound characteristics are compatible with a cyst. In case the needle has to transpass the pleural folds during either EUS-FNA or EBUS-TBNA, there is a risk for *pneumothorax*. Although the risk is minimal, it is not absent and should be taken into account, especially when patients with severe emphysema are investigated. *Bleeding* is manageable

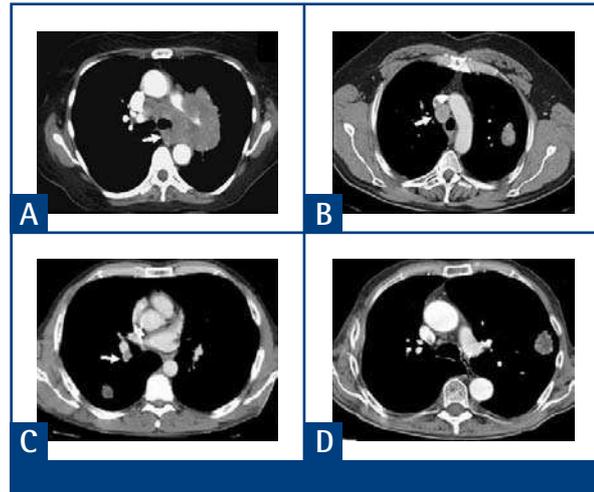


Figure 3. ACCP definition of patients with non-small cell lung cancer needing mediastinal investigation.

when anti-coagulants and anti-platelet therapy (except low dose aspirin) are withdrawn and coagulation tests are performed on indication. *Oesophageal perforation* has been reported for EUS-FNA in a series of mesothelioma patients.²⁸

The risk of *false positive needle aspiration* has also been described.²⁹ In case of a centrally located parenchymal tumour one has to be very careful not to sample the primary tumour instead of a mediastinal lymph node. The absence of lymphocytes or the presence of a small amount of lymphocytes does not ascertain or exclude that parenchymal tumour has been sampled. A subsequent invasive mediastinal test is required if there is any doubt.

Quality criteria for FNA and/or TBNA samples

If ROSE is available, air dried smears are stained immediately and evaluated for their representativity. ROSE avoids the endoscopist to perform futile biopsies hereby shortening the procedure and minimizing the risk for complications.⁵ It remains unproven whether ROSE by a cytotechnician or cytopathologist really adds to the accuracy of both techniques. If ROSE is not available, the Belgian working party advises 3 punctures per lymph node station or lesion. In that case, samples can be processed as conventional smears (e.g. air dried or spray-fixed) or rinsed into a liquid preservative collection medium (liquid based preparation).

The pathological analysis of the acquired samples is of eminent importance. The pathology report should at least mention if the samples are representative,

and if a qualifying conclusion can be made or not. In addition to conventional cytology, immunohistochemistry and molecular assays can be performed on the samples. For the latter, liquid based preparations are preferable. The choice of the additional stains is governed by the indication and differential diagnosis.

What if no qualifying diagnosis or staging is obtained with EUS-FNA or EBUS-TBNA?

The clinician will regularly be confronted with a “negative” or “non-diagnostic” result after EUS-FNA or EBUS-TBNA. Because EUS-FNA and EBUS-TBNA can be used either for diagnostic or for staging indications, it is important to consider what to do in each situation and to integrate this result with the other available data. However, based on the available reports, it is obvious that the negative predictive value of EUS-FNA and EBUS-TBNA is lower than 90-95% in most situations.^{16,30}

An EUS-FNA or EBUS-TBNA can be “false” negative for several reasons. Firstly, when *no representative samples* are obtained the result is prone for false negativity. For a lymph node, the presence of lymphocytes in the samples is a prerequisite. For parenchymal lung lesions, there is no definition available of what a representative sample must contain. In line with this, the limited diagnostic range of fine needle cytology can make the final report by the pathologist *not conclusive*. The latter is especially true for non-carcinoma pathology such as lymphoma. Secondly, an *anatomic miss* which means that the wrong lesion is sampled, is an obvious reason. Thirdly, a *sampling error in the target lesion* (e.g. micrometastatic tumour islets) and fourthly an *analysis error* (e.g. scarce tumour cells in the numerous samples) can also be the reason for a false negative result.

In general, it can be advised advice to confirm a non-diagnostic or negative result with an adequate subsequent procedure (evidence moderate, benefit outweighs risk and harm, recommendation level 1B). The procedure of choice after a negative EUS-FNA or EBUS-TBNA depends on the localisation of the lesion, the availability of “alternate” techniques and the differential diagnosis.

Implementation and impact of EUS-FNA and EBUS-TBNA

Since both EUS-FNA and EBUS-TBNA are applicable for a considerable amount of chest disorders,

implementation of these techniques by chest physicians will become increasingly important. A recent study compared the results of EUS-FNA performed by chest physicians in a university training centre versus non-university centres and showed that, after an appropriate training, no differences were observed in accuracy (*ATS 2008 Abstract; Annema J*). Although there are indirect data about learning curves for blind TBNA, there are no formal guidelines available on how chest physicians should be trained for endoscopic ultrasound techniques. Nevertheless, it seems reasonable to stimulate a training course for chest physicians with hands-on not only for EUS-FNA but also for EBUS-TBNA (evidence moderate, benefit outweighs risk and harm, recommendation level 1B). This relates not only to the accuracy issue, but also to the safety and avoidance of severe complications. Accordingly, and although no formal numbers exist, a minimal number of procedures should be performed yearly in order to maintain skills and highest accuracy and safety levels achievable.

Concerning impact, it has been demonstrated that for both diagnostic and staging indication, implementation of EUS-FNA or EBUS-TBNA are validated alternate procedures in up to 70% of the patients.^{17,18,29} This is of potential interest since implementation of EUS-FNA or EBUS-TBNA can avoid risks associated with general anaesthesia, surgical interventions or transthoracic punctures. In addition, since EUS-FNA and EBUS-TBNA are minimally invasive techniques that do not require an in-hospital stay, they hold promise to be cost saving. However, the latter issue is a matter of debate because negative findings still need (often surgical) confirmation which is cost-generating.

Conclusion

EUS-FNA and EBUS-TBNA are two minimally invasive out-patient techniques available to obtain diagnosis of intrathoracic lesions or to perform mediastinal staging in patients with NSCLC. The procedures are safe when performed by adequately trained chest physicians that have a good knowledge of the indications, contraindications and limitations of these procedures. Both EUS-FNA and EBUS-TBNA have shown to impact pulmonary medicine in a substantial amount of the patients, especially in terms of avoiding surgical interventions. Endoscopic ultrasound is currently positioned as an alternate adjunct procedure in pulmonary medicine which does not replace other techniques.

Key messages for clinical practice

1. EUS-FNA and EBUS-TBNA are two endoscopic ultrasound techniques that allow the real time guided transoesophageal or transbronchial puncture of thoracic lesions and lymph nodes.
2. EUS-FNA and EBUS-TBNA are techniques performed without general anaesthesia, and in an out-patient setting.
3. The implementation of EUS-FNA and EBUS-TBNA for diagnosis and staging intrathoracic malignancies is supported by a substantial body of clinical evidence.
4. The implementation of EUS-FNA and EBUS-TBNA by chest physicians has a measurable clinical impact mainly in terms of avoided surgical diagnostic procedures.
5. Chest physicians should consider learning EUS-FNA and EBUS-TBNA.

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References

1. McCrory DC, Lewis SZ, Heitzer J et al. Methodology for lung cancer evidence review and guideline development: ACCP evidence-based clinical practice guidelines (2nd Edition). *Chest* 2007;132(3 Suppl):23S-28S.
2. Herth FJ, Krasnik M, Yasufuku K et al. Endobronchial Ultrasound-guided Transbronchial Needle Aspiration. *J Bronchol* 2006;13(2):84-91.
3. Kramer H, van Putten JW, Douma WR et al. Technical description of endoscopic ultrasonography with fine-needle aspiration for the staging of lung cancer. *Respir Med* 2005;99(2):179-185.
4. Tournoy KG, Praet MM, Van Maele G et al. Esophageal endoscopic ultrasound with fine-needle aspiration with an on-site cytopathologist: high accuracy for the diagnosis of mediastinal lymphadenopathy. *Chest* 2005;128(4):3004-3009.
5. Baram D, Garcia RB, Richman PS. Impact of rapid on-site cytologic evaluation during transbronchial needle aspiration. *Chest* 2005;128(2):869-875.
6. Lee HS, Lee GK, Lee HS et al. Real-time Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in Mediastinal Staging of Non-Small Cell Lung Cancer: How Many Aspirations Per Target Lymph Node Station? *Chest* 2008;134(2):368-374.
7. Annema JT, Veselic M, Rabe KF. EUS-guided FNA of centrally located lung tumours following a non-diagnostic bronchoscopy. *Lung Cancer* 2005;48(3):357-361.
8. Tournoy KG, Rintoul RC, van Meerbeeck JP et al. EBUS-TBNA for the diagnosis of central parenchymal lung lesions not visible at routine bronchoscopy. *Lung Cancer* 2008;doi:10.1016/j.lungcan.2008.04.004.
9. Bauwens O, Dusart M, Pierard P et al. Endobronchial ultrasound and value of PET for prediction of pathological results of mediastinal hot spots in lung cancer patients. *Lung Cancer* 2008;61:356-361.
10. Herth FJ, Eberhardt R, Vilmann P et al. Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. *Thorax* 2006;61(9):795-798.
11. Wong M, Yasufuku K, Nakajima T et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. *Eur Respir J* 2007;29(6):1182-1186.
12. Annema JT, Veselic M, Rabe KF. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of sarcoidosis. *Eur Respir J* 2005;25(3):405-409.
13. Herth FJ, Morgan RK, Eberhardt R et al. Endobronchial ultrasound-guided miniforceps biopsy in the biopsy of subcarinal masses in patients with low likelihood of non-small cell lung cancer. *Ann Thorac Surg* 2008;85(6):1874-1878.
14. Eloubeidi MA, Seewald S, Tamhane A et al. EUS-guided FNA of the left adrenal gland in patients with thoracic or GI malignancies. *Gastrointest Endosc* 2004;59(6):627-633.
15. Kramer H, Koeter GH, Sleijfer DT et al. Endoscopic ultrasound-guided fine-needle aspiration in patients with mediastinal abnormalities and previous extrathoracic malignancy. *Eur J Cancer* 2004;40(4):559-562.
16. Detterbeck FC, Jantz MA, Wallace MB et al. Invasive mediastinal staging of lung cancer. ACCP Evidence based

clinical practice guidelines (2nd edition). *Chest* 2007;132(3 suppl):202S-220S

17. Tournoy KG, De RF, Vanwalleghem LR et al. Endoscopic ultrasound reduces surgical mediastinal staging in lung cancer: a randomized trial. *Am J Respir Crit Care Med* 2008; 77(5):531-535.

18. Yasufuku K, Chiyo M, Koh E et al. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. *Lung Cancer* 2005;50(3):347-354.

19. De Leyn P, Lardinois D, Van Schil PE et al. ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. *Eur J Cardiothorac Surg* 2007;32:1-8.

20. Wallace MB, Pascual JM, Raimondo M et al. Minimally invasive endoscopic staging of suspected lung cancer. *JAMA* 2008;299(5):540-546.

21. Robinson LA, Ruckdeschel JC, Wagner H, Jr. et al. Treatment of non-small cell lung cancer stage IIIA. *Chest*

2007;132:243S-265S.

22. Herth FJ, Ernst A, Eberhardt R et al. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum. *Eur Respir J* 2006;28(5):910-914.

23. Herth FJ, Eberhardt R, Krasnik M et al. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically and positron emission tomography-normal mediastinum in patients with lung cancer. *Chest* 2008;133(4):887-891.

24. Tournoy KG, Ryck FD, Vanwalleghem L et al. The yield of endoscopic ultrasound in lung cancer staging: does lymph node size matter? *J Thorac Oncol* 2008;3(3):245-249.

25. Herth FJ, Annema JT, Eberhardt R et al. Endobronchial Ultrasound With Transbronchial Needle Aspiration for Restaging the Mediastinum in Lung Cancer. *J Clin Oncol* 2008;26:3346-3350.

26. Annema JT, Veselic M, Versteegh MI et al. Mediastinal restaging: EUS-FNA offers a new perspective. *Lung Cancer* 2003;42(3):311-318.

27. Al-Haddad M, Wallace MB, Woodward TA et al. The safety of fine-needle aspiration guided by endoscopic ultrasound: a prospective study. *Endoscopy* 2008;40:204-208.

28. Tournoy KG, Burgers SA, Annema JT et al. Transesophageal endoscopic ultrasound with fine needle aspiration in the preoperative staging of malignant pleural mesothelioma. *Clin Cancer Res* 2008;14(19):6259-6263.

29. Annema JT, Versteegh MI, Veselic M et al. Endoscopic ultrasound added to mediastinoscopy for preoperative staging of patients with lung cancer. *JAMA* 2005;294(8):931-936.

30. Herth FJ, Rabe KF, Gasparini S et al. Transbronchial and transoesophageal (ultrasound-guided) needle aspirations for the analysis of mediastinal lesions. *Eur Respir J* 2006;28(6):1264-1275.

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